

**Amendments to the Claims:**

This listing of claims will replace all prior version, and listings, of claims in the application:

**Listing of Claims:**

1. (Currently Amended) An isolated nucleic acid molecule encoding a splice variant of a gene sequence capable of being spliced to result in a reference human telomerase encoding ~~[[of]]~~ SEQ ID No: 2, wherein the splice variant has at least one of the following insertions or deletions:

(a) an insertion of sequence X (comprising SEQ ID No: 32) at nucleotide 1766 of SEQ ID No: 1;

(b) an insertion of nucleic acid sequence encoding sequence 1 (SEQ ID NO: 24) at nucleotide 1950 of SEQ ID No: 1;

(c) a deletion of nucleotides 2131 through 2166 of SEQ ID No: 1;

(d) a deletion of nucleotides 2287 through 2468 of SEQ ID No: 1;

(e) an insertion of sequence 2 comprising SEQ ID No: 29 at nucleotide 2843 of SEQ ID No: 1; and

(f) an insertion of nucleic acid sequence encoding sequence 3 (SEQ ID No: 31) at nucleotide 3157 of SEQ ID No: 1.

and wherein the splice variant does not encode SEQ ID No: 2.

2. (Canceled).

3. (Canceled)

4. (Currently Amended) The nucleic acid molecule of claim 1, wherein the nucleic acid molecule encodes one of ~~the amino acid sequence presented in Figure 11 (SEQ ID Nos: 35, 37, 39, 42, 44, 46, 48, 50, 52-54, 56-58, 60-62, 64-66, 68-70, 72-74, 76-78, 80-82, 84-86), or variant thereof, wherein said variant has at least 75% amino acid identity with said amino acid sequences presented in Figure 11.~~

5. (Currently Amended) An isolated nucleic acid molecule encoding any ~~of the amino acid sequences presented in Figure 11 (SEQ ID Nos: 35, 37, 39, 42, 44, 46, 48, 50, 56-58, 60-62, 64-66, 68-70, 72-74, 76-78, 80-82, 84-86), or which hybridizes under the following stringency conditions: 1 M Na<sup>+</sup> at 65°C; 5X SSPE, 0.5% SDS, 5X Denhardt's~~

~~solution to the complement of one of the sequences thereof, provided that the nucleic acid molecule is not EST AA281296 or a variant thereof.~~

wherein said variant has at least 95% amino acid identity with said amino acid sequences and binds telomerase RNA (hTR) or has telomerase activity; and

wherein the nucleic acid does not encode SEQ ID No: 2.

6. (Currently Amended) An isolated nucleic acid molecule ~~comprising~~ consisting of any of the sequences presented in Figure 10 (SEQ ID Nos.: ~~[[18,]] 23, 25, 27, 29, 30, 32, 33), or which hybridizes under the following stringency conditions: 1 M Na<sup>+</sup> at 65°C; 5X SSPE, 0.5% SDS, 5X Denhardt's solution to the complement of one of the sequences thereof, or the complement thereof.~~

7. (Withdrawn): An oligonucleotide comprising from 10 to 100 contiguous nucleotides from the sequence presented in Figure 1 or its complement.

8. (Withdrawn): An oligonucleotide comprising from 10 to 100 contiguous nucleotides from the sequences presented in Figure 10 or the complements thereof.

9. (Withdrawn): The oligonucleotide of either of claims 7 or 8, wherein the oligonucleotide is labeled.

10. (Withdrawn): The oligonucleotide of claim 9, wherein the label is a radiolabel, a chemiluminescent label, or biotin.

11. (Currently Amended) An expression vector, comprising a heterologous promoter operably linked to a nucleic acid molecule according to any of claims 1, ~~[[2, and]] 4-6, and 109.~~

12. (Original): The expression vector of claim 11, wherein the vector is selected from the group consisting of bacterial vectors, retroviral vectors, adenoviral vectors and yeast vectors.

13. (Previously presented): A host cell containing a vector according to claim 11.

14. (Original): The host cell of claim 13, wherein the cell is selected from the group consisting of human cell, monkey cell, mouse cell, rat cell, yeast cell and bacterial

cell.

15. (Original): The host cell of claim 13, wherein the cell is a human cell.
16. (Withdrawn): An isolated protein comprising a vertebrate telomerase protein.
17. (Withdrawn): The protein of claim 16, wherein the vertebrate is a human.
18. (Withdrawn): The protein of claim 16, wherein the protein comprises the amino acid sequence presented in Figure 1 or 11, or variant thereof.
19. (Withdrawn): A portion of a vertebrate telomerase protein.
20. (Withdrawn): The portion of claim 19, wherein the amino acid sequence of the portion is presented in Figure 1.
21. (Withdrawn): The portion of claim 19, wherein the amino acid sequence of the portion is presented in Figure 11.
22. (Withdrawn): The portion of claim 19, wherein the portion is from 10 to 100 amino acids long.
23. (Withdrawn): An antibody that specifically binds to the protein according to either claim 16 or 19.
24. (Withdrawn): An antibody that specifically binds to a polypeptide encoded by a sequence selected from the group consisting of region 1, region  $\alpha$ , region  $\beta$ , region 2 and region 3.
25. (Withdrawn): The antibody according to claim 24, wherein the antibody is a monoclonal antibody.
26. (Withdrawn): A hybridoma that produces an antibody according to claim 14.
27. (Currently Amended) A nucleic acid probe that is capable of specifically hybridizing to a nucleic acid molecule encoding a splice variant of human telomerase according to claim 1 ~~under the following stringency conditions: 1 M Na<sup>+</sup> at 65°C;~~

~~5X SSPE, 0.5% SDS, 5X Denhardt's solution at 65°C,~~

wherein the probe consists of one of SEQ ID Nos: 23, 25, 27, 29, 30, 32 or 33  
or the complement thereof;

or a fragment of SEQ ID Nos: 23, 29, 30, 31 or 32 or the complement thereof.

28. (Currently Amended) The probe of claim 27, wherein the fragment ~~probe~~ is from 12 to 200 nucleotides long.

29. (Currently Amended) The probe of claim 27, wherein the fragment ~~probe~~ is from 20 to 50 nucleotides long.

30. (Withdrawn): The probe of claim 17, wherein the nucleic acid molecule has the sequence presented in Figure 1 or its complement thereof.

31. (Previously presented): The probe of claim 27, wherein the nucleic acid molecule is labeled.

32. (Canceled)

33. (Withdrawn): The primers of claim 32, wherein the nucleic acid molecule comprises the sequence presented in Figure 1 or its complement.

34. (Canceled)

35. (Withdrawn): The primers of claim 32, wherein the pair of primers is capable of specifically amplifying sequence comprising all or a part of region 1, region  $\alpha$ , region  $\beta$ , region 2, region 3 region X or region Y.

36. (Withdrawn): The primers of claim 35, wherein the primers flank nucleotide 222, 1950, 2131-2166, 2287-2468, 2843, or 3157 as presented in Figure 1.

37. (Withdrawn): The primers of claim 36, wherein only one of each primer pair flanks nucleotide 222, 1950, 2131-2166, 2287-2468, 2843, or 3157 as presented in Figure 1 and the other primer of the pair has sequence corresponding to one of the sequences presented in Figure 10 or complements thereof.

38. (Withdrawn): A pair of oligoprimers capable of specifically amplifying genomic sequence presented in Figure 10, wherein the primers amplify more than nucleotides 1 to 38.

39. (Withdrawn): An oligonucleotide that hybridizes specifically to a nucleic acid sequence in region 1, region  $\alpha$ , region  $\beta$ , region 2, region 3 region X or region Y.

40. (Withdrawn): The oligonucleotide of claim 39, wherein the oligonucleotide is from 15 to 36 bases.

41. (Withdrawn): A method of diagnosing cancer in a patient, comprising preparing tumor cDNA and amplifying the tumor cDNA using primers that specifically amplify human telomerase nucleic acid sequence, wherein the detection of telomerase nucleic acid sequences is indicative of a diagnosis of cancer.

42. (Withdrawn): The method of claim 41, further comprising comparing the amount of amplified telomerase sequence to a control, wherein increase telomerase nucleic acid sequences over the control is indicative of a diagnosis of cancer.

43. (Withdrawn): The method of claim 41, wherein the primers span region 1, region  $\alpha$ , region  $\beta$ , region 2, region 3 region X or region Y, wherein the pattern of amplification is indicative of a diagnoses of cancer.

44. (Withdrawn): The method of claim 43, wherein the primers are Htel Intron T and Htel 723B.

45. (Withdrawn): The method of claim 44, wherein the primers are Htel335T and Htel1022B.

46. (Withdrawn): A method of determining a pattern of telomerase RNA expression in cells, comprising preparing cDNA from mRNA isolated from the cells, amplifying the cDNA using primers according to claim 35, therefrom determining the pattern of telomerase RNA expression.

47. (Withdrawn): The method of claim 46, further comprising detecting the amplified product by hybridization with an oligonucleotide having all or part of the sequence of region 1, region  $\alpha$ , region  $\beta$ , region 2, region 3 region X or region Y.

48. (Withdrawn): A method of diagnosing cancer in a patient, comprising determining a pattern of telomerase RNA expression, comprising amplifying telomerase from cDNA synthesized from tumor RNA, and detecting the amplified product by hybridization with an oligonucleotide having all or part of the sequence of region 1, region  $\alpha$ , region  $\beta$ , region 2, region 3 region X or region Y, therefrom determining the pattern of telomerase

RNA expression, wherein the pattern is indicative of a diagnosis of cancer.

49. (Withdrawn): The method of claim 48, further comprising comparing the pattern to a pattern obtained from a reference cancer.

50. (Withdrawn): A non-human transgenic animal whose cells contain a vertebrate telomerase gene that is operably linked to a promoter effective for the expression of the gene.

51. (Withdrawn): The animal of claim 50, wherein the animal is a mouse.

52. (Withdrawn): The animal of claim 50, wherein the promoter is tissue-specific.

53. (Withdrawn): The animal of claim 50, wherein the telomerase gene is any of the nucleic acid sequences presented in Figure 11.

54. (Withdrawn): A mouse, whose cells have an endogenous telomerase gene disrupted by homologous recombination with a nonfunctional telomerase gene, wherein the mouse is unable to express endogenous telomerase .

55. (Withdrawn): An inhibitor of vertebrate telomerase activity, wherein the inhibitor binds to telomerase and is not a nucleoside analogue.

56. (Withdrawn): The inhibitor of claim 55, wherein the vertebrate is a human.

57. (Withdrawn): The inhibitor of claim 55, wherein the inhibitor is antisense nucleic acid complementary to human telomerase mRNA.

58. (Withdrawn): The inhibitor of claim 57, wherein the antisense is complementary to region  $\alpha$ , region  $\beta$ , region 2, region 3 or region X.

59. (Withdrawn): The inhibitor of claim 55, wherein the inhibitor is a ribozyme.

60. (Withdrawn): A method of treating cancer, comprising administering to a patient a therapeutically effective amount of an inhibitor according to claim 55.

61. (Currently Amended): An isolated nucleic acid molecule consisting of ~~comprising~~ a sequence selected from the group consisting of region 1 (SEQ ID No:23), region

$\alpha$  (SEQ ID No:25), region  $\beta$  (SEQ ID No:27), region 2 (SEQ ID No:29) and region 3 (SEQ ID No:30) ~~as presented in Figure 10 and variants thereof, wherein said variant has at least 75% nucleotide identity with the nucleic acid sequences presented in Figure 11.~~

62. (Withdrawn): A method of identifying an effector of telomerase activity comprising:

- (a) adding a candidate effector to a mixture of telomerase protein, RNA component and template, wherein the telomerase protein is encoded by an isolated nucleic acid molecule according to claim 1;
- (b) detecting telomerase activity; and
- (c) comparing the amount of activity in step (b) to the amount of activity in a control mixture without candidate effector, therefrom identifying an effector.

63. (Withdrawn): The method of claim 62, wherein the effector is an inhibitor.

64. (Withdrawn): the method of claim 62, wherein the nucleic acid molecule encodes human telomerase.

65. (Canceled)

66. (Canceled)

67. (Currently Amended): The nucleic acid molecule of claim 1, [[65]], wherein the splice variant of human telomerase has at least a deletion of nucleotides 2131-2166 of SEQ ID No: 1 ~~lacks nucleotide sequence encoding RTase motif A.~~

68. (Withdrawn): The nucleic acid molecule of any one of claims 65-67, wherein the splice variant of human telomerase lacks nucleotide sequence encoding a P-loop motif.

69. (Withdrawn): The nucleic acid molecule of any one of claims 65-68, wherein the splice variant of human telomerase lacks the C-terminal domain of the reference human telomerase.

70. (Withdrawn): The nucleic acid molecule of any one of claims 65-69, wherein the splice variant of human telomerase has an altered C-terminus comprising sequence encoding a consensus SH3 binding site.

71. (Canceled)

72. (Canceled)

73. (Currently Amended): The complement of the nucleic acid molecules [molecule] of any of claims 1, 4, 5, 6 and 109. ~~claim 65.~~

74. (Currently Amended): The nucleic acid molecule of any of claims 1, 4, 5, 6 and 109 ~~claim 65~~, wherein said molecule is a DNA molecule.

75. (Currently Amended): The nucleic acid molecule of any of claims 1, 4, 5, 6 and 109 ~~claim 65~~, wherein said molecule is an RNA or cDNA molecule.

Claims 76-85. (Canceled)

86. (Withdrawn): An oligonucleotide comprising 15-100 contiguous nucleotides of one of the sequences presented in Figure 10 (SEQ ID Nos: 18, 23, 25, 27, 29, 30, 32, 33) or the complements thereof.

87. (Withdrawn): The oligonucleotide of claim 86, wherein the oligonucleotide is from 15 to 36 nucleotides long.

88. (Previously presented): The oligonucleotide of claim 86, wherein the oligonucleotide is from 20 to 50 nucleotides long.

89. (Withdrawn): The oligonucleotide of claim 86, wherein the oligonucleotide is labeled.

90. (Withdrawn): The oligonucleotide of claim 89, wherein the label is a radiolabel, a chemiluminescent label, or biotin.

91. (Withdrawn): A pair of oligonucleotide primers that amplify sequence selected from the group consisting of region 1 (SEQ ID No: 23), region  $\alpha$  (SEQ ID No: 25), region  $\beta$  (SEQ ID No: 27), region 2 (SEQ ID No: 29), region 3 (SEQ ID No: 30), region X (SEQ ID No: 32) or region Y (SEQ ID No: 18).

92. (Canceled)

93. (Currently Amended): A pair of oligonucleotide primers that amplify nucleic acid sequence of human telomerase containing a splice junction, wherein only one primer of each primer pair flanks nucleotide ~~222~~-1950, 2131-2166, 2287-2468, 2843, or 3157

as presented in Figure 1 (SEQ ID No: 1) and the other primer of the pair has sequence corresponding to all or a portion of one of the sequences presented in Figure 10 (SEQ ID Nos: 18, 23, 25, 27, 29, 30, 32, 33) or complements thereof.

94. (Withdrawn): A method of diagnosing cancer in a patient, comprising preparing tumor cDNA and amplifying the tumor cDNA using a pair of oligonucleotide primers that amplify sequence selected from the group consisting of region 1 (SEQ ID No: 23), region  $\alpha$  (SEQ ID No: 25), region  $\beta$  (SEQ ID No: 27), region 2 (SEQ ID No: 29), region 3 (SEQ ID No: 30), region X (SEQ ID No: 32) or region Y (SEQ ID No: 18), wherein the pattern of amplification is indicative of a diagnosis of cancer.

95. (Withdrawn): A method of diagnosing cancer in a patient, comprising preparing tumor cDNA and amplifying the tumor cDNA using a pair of oligonucleotide primers that amplify sequence of human telomerase containing a splice junction, wherein the primer pair flanks nucleotide 222, 1950, 2131-2166, 2287-2468, 2843, or 3157 as presented in Figure 1 (SEQ ID No: 1), wherein the pattern of amplification is indicative of a diagnosis of cancer.

96. (Withdrawn): A method of diagnosing cancer in a patient, comprising preparing tumor cDNA and amplifying the tumor cDNA using a pair of oligonucleotide primers that amplify sequence of human telomerase containing a splice junction, wherein only one primer of each primer pair flanks nucleotide 222, 1950, 2131-2166, 2287-2468, 2843, or 3157 as presented in Figure 1 (SEQ ID No: 1) and the other primer of the pair has sequence corresponding to all or a portion of one of the sequences presented in Figure 10 (SEQ ID Nos: 18, 23, 25, 27, 29, 30, 32, 33) or complements thereof.

97. (Withdrawn): A method of determining a pattern of telomerase RNA expression in cells, comprising,

preparing cDNA from mRNA isolated from the cells,

amplifying the cDNA using primers that amplify a splice variant of nucleic acid encoding human telomerase and

detecting the amplified product by hybridization with all or part of the sequence of region 1 (SEQ ID No: 23), all or part of the sequence of region  $\alpha$  (SEQ ID No: 25), all or part of the sequence of region  $\beta$  (SEQ ID No: 27), all or part of the sequence of region 2 (SEQ ID No: 29), all or part of the sequence of region 3 (SEQ ID No: 30), all or part of the sequence of region X (SEQ ID No: 32) or all or part of the sequence of region Y (SEQ

ID No: 18);

therefrom determining the pattern of telomerase RNA expression.

98. (Withdrawn): A method of diagnosing cancer in a patient by determining a pattern of telomerase RNA expression, comprising,

amplifying sequence of human telomerase from cDNA synthesized from tumor RNA using primers that amplify a splice variant of human telomerase, and

detecting the amplified product by hybridization with all or part of the sequence of region 1 (SEQ ID No: 23), all or part of the sequence of region  $\alpha$  (SEQ ID No: 25), all or part of the sequence of region  $\beta$  (SEQ ID No: 27), all or part of the sequence of region 2 (SEQ ID No: 29), all or part of the sequence of region 3 (SEQ ID No: 30), all or part of the sequence of region X (SEQ ID No: 32) or all or part of the sequence of region Y (SEQ ID No: 18),

therefrom determining the pattern of telomerase RNA expression, wherein the pattern is indicative of a diagnosis of cancer.

99. (Withdrawn): The method of claim 98, further comprising comparing the pattern to a pattern obtained from a reference cancer.

100. (Withdrawn): A nucleic acid molecule encoding a human telomerase that lacks RTase motifs A, B, C, and D.

101. (Canceled)

102. (Withdrawn): The nucleic acid molecule of either of claims 101 or 102, wherein the human telomerase lacks a P-loop motif.

103. (Withdrawn): The nucleic acid molecule of either of claims 101 or 102, wherein the human telomerase has an altered C-terminal domain comprising a consensus SH3 binding site.

104. (Withdrawn): The nucleic acid molecule of either one of claims 101 or 102, wherein the human telomerase lacks the C-terminal domain of the human telomerase presented in SEQ ID No. 2.

105. (Withdrawn): A nucleic acid molecule encoding a human telomerase that lacks a P-loop motif.

106. (Withdrawn): A nucleic acid molecule encoding a human telomerase that has an altered C-terminal domain comprising a consensus SH3 binding site.

107. (Withdrawn): A nucleic acid molecule encoding a human telomerase that lacks the C-terminal domain of the human telomerase presented in SEQ ID No. 2.

108. (New) An isolated nucleic acid molecule encoding any of SEQ ID Nos.: 24, 26, 28, or 31.

109. (New) The probe of claim 31, wherein the label is a chemiluminescent label, a radioactive label, or biotin.

110. (New) The nucleic acid molecule of claim 1, wherein the splice variant of human telomerase has at least an insertion of nucleic acid sequence encoding sequence 3 (SEQ ID No:31) at nucleotide 3157 of SEQ ID No: 1

111. (New) An oligonucleotide consisting of 15-100 contiguous nucleotides of one of the sequences selected from the group consisting of SEQ ID Nos. 23, 29, 30, 32, 33 or the complements thereof.

112. (New) The oligonucleotide of claim 111, wherein the oligonucleotide is labeled.

113. (New) The oligonucleotide of claim 112, wherein the label is a radiolabel, a chemiluminescent label, or biotin.

114. (New) A pair of oligonucleotide primers that amplify sequence selected from the group consisting of region 1 (SEQ ID No: 23), region  $\alpha$  (SEQ ID No: 25), region  $\beta$  (SEQ ID No: 27), region 2 (SEQ ID No: 29), region 3 (SEQ ID No: 30), region X (SEQ ID No: 32), wherein the primers comprise at least 15 contiguous nucleotides of one of SEQ ID Nos: 23, 25, 27, 29, 30, 32, or 18 or complements thereof and wherein the primers are from 15 to 50 nucleotides in length.

115. (New) A method of determining a pattern of telomerase RNA expression in cells, comprising,

(a) preparing cDNA from mRNA isolated from the cells,

(b) amplifying the cDNA using primers that amplify a splice variant of nucleic acid encoding human telomerase to form an amplified product and

(c) hybridizing the amplified product with one or more of the following :

all or at least 15 contiguous nucleotides of the sequence of region 1 (SEQ ID No: 23), all or at least 15 contiguous nucleotides of the sequence of region  $\beta$  (SEQ ID No: 27), all or at least 15 contiguous nucleotides of the sequence of region 2 (SEQ ID No: 29), all or at least 15 contiguous nucleotides of the sequence of region 3 (SEQ ID No: 30), or all or at least 15 contiguous nucleotides of the sequence of region X (SEQ ID No: 32); or a complement thereof; and

(d) detecting hybridization;

therefrom determining the pattern of telomerase RNA expression.

116. (New) A method of determining a pattern of telomerase RNA expression in cells, comprising,

(a) preparing cDNA from mRNA isolated from the cells,

(b) amplifying the cDNA using primers that amplify a splice variant of nucleic acid encoding human telomerase to form an amplified product and

(c) hybridizing the amplified product with two or more of the following:

all or at least 15 contiguous nucleotides of the sequence of region 1 (SEQ ID No: 23), all or at least 15 contiguous nucleotides of the sequence of region  $\alpha$  (SEQ ID No: 25), all or at least 15 contiguous nucleotides of the sequence of region  $\beta$  (SEQ ID No: 27), all or at least 15 contiguous nucleotides of the sequence of region 2 (SEQ ID No: 29), all or at least 15 contiguous nucleotides of the sequence of region 3 (SEQ ID No: 30), all or at least 15 contiguous nucleotides of the sequence of region X (SEQ ID No: 32) or all or at least 15 contiguous nucleotides of the sequence of region Y (SEQ ID No: 18); or a complement thereof; and

(d) detecting hybridization;

therefrom determining the pattern of telomerase RNA expression.

117 (New) The method of either of claims 115 or 116, wherein the contiguous nucleotides contain a label.

118. (New) The method of claim 117, wherein the label is radioactive, chemiluminescent, or biotin.

**Amendments to the Drawings:**

The attached sheets of drawings include changes to Figs. 11A-C, 11G-N and 11R-W. These sheets replace the original sheets for these figures. In addition to the changes made in the drawings submitted 27 March, 2003, and accepted by the Examiner in Paper No. 22, residue 806 has been corrected in Figures 11C and 11N. Residue 806 was previously erroneously identified as V (Val) and now has been corrected to G (Gly). A minor change is also made to the title of Figures 11 A and L to clarify the type of truncation presented therein. All changes have been marked-up in red on the annotated sheets showing changes.

Attachment: Replacement Sheets Figs. 11A-C, 11G-N and 11R-W  
Annotated Sheets Showing Changes in Figs. 11A-C, 11G-N and 11R-W

## REMARKS

Reconsideration of this Application is respectfully requested. Claims 1-118 are pending; of these, claims 1, 4, 5, 6, 11, 27-29, 61, 67, 74, 75, and 93 are currently amended; claims 12, 14, and 15 are original; claims 13, 31, and 88 are previously presented; claims 108-118 are new; claims 2, 3, 32, 34, 65, 66, 71, 72, 76-85, 92, and 101 are canceled; and claims 7-10, 16-26, 35-60, 62-64, 68-70, 86, 87, 89-91, 94-100, and 102-107 are withdrawn. No new matter is added by the claim amendments. The Remarks below are directed to the objections and rejections of the outstanding Office Action.

The Owner of the application thanks Examiners Prouty and Walicka for the Telephone Interviews of 18 and 22 August 2003, and is grateful for their thoughtful input. In this response, claims have been amended on the basis of those discussions and in the interest of advancing to an allowance. Specific arguments below detail why the Owner disagrees with the Office's rejections in Paper No. 22, especially with regard to lack of written description and lack of enablement.

### 1.1 Remarks about the Objections to the Specification

The Owner acknowledges in Paper No. 22 that the Examiner has removed objections to Table 1 of the specification and to motifs B, C, and D.

*Objection 1:* The Examiner objects to the specification for unclear description of motif A.

*Remark:* As the Examiner points out on pages 2-3 of the Office Action, the boundaries of motif A (amino acids 708-720) are not identical to sequence alpha (amino acids 711-722). The Specification has been amended to recite that deletion of sequence alpha deletes "nearly all of" motif A. This amendment does not add new matter, but merely clarifies the relationship of sequence alpha and motif A. The Owner respectfully requests that the Examiner withdraw the objection.

*Objection 2:* The Examiner objects to parts of the specification that lack sequence identification numbers for certain primers and other sequences.

*Remarks:* By the Amendments to the specification enumerated above, the Owner has inserted the appropriate sequence identifiers in the text. The Owner respectfully requests that the Examiner withdraw the objection.

*Objection 3:* The Examiner objects to Table 1 as being an incomplete listing of every splice variant.

*Remarks:* As explained in the specification, Table 1 is a representation of the splice variants and reference telomerase sequences presented in Figure 11. As such, the Table displays which exons are in a set of exemplary sequences of human telomerase. In addition to Table 1, the specification teaches many more splice variants. There is no requirement that every single variant be presented as a representation, such as in Table 1. In the recent telephone interviews, the Examiner indicated that amending Table 1 would not be necessary. Thus, the Examiner is requested to remove the objection.

*Objections 4 and 5:* The Examiner objects to SEQ ID Nos: 35 and 52 being described as “N-terminal” truncated telomerases, believing that the sequences are “C-terminal” truncations.

*Remarks:* The use of exon X in the splice variants presented in SEQ ID Nos: 35 and 52 result in truncation after 588 amino acids (for ID No: 35) and 622 amino acids for ID No: 52. The truncation occurs therefore in the N-terminal domain of the protein (specification page 11). For clarification, the titles of Figures 11 A and L have been changed to reflect this meaning. Therefore, Owner respectfully requests that the Examiner accept the changes made to the Figures and withdraw the objection.

## **1.2 Remarks about the Objections to the Drawings**

*Objection:* The Examiner objects to the drawings of Figure 11 because of an error of amino acid residue 806 of SEQ ID NO: 39.

*Remarks:* The Drawings for Figure 11 have been amended to correct the error in amino acid residue 806, the penultimate amino acid. Submitted herewith are marked-up Figure 11 showing the changes in red and clean drawings of Figure 11. New matter is not added with this correction. As discussed in the Declaration of Andrzej Kilian (“Declaration”), the error in this sequence, as well as the equivalent error in SEQ ID Nos: 60-62, was inadvertent and arose because of a clerical error. Specifically, the nucleotide codons in SEQ ID NO:38 and 59 are correct and are listed correctly in Figures 11C and N. The codons are for glycine. In the Figures and in the Sequence Listing, however, the penultimate amino acid is incorrectly given as “Val”. This was a clerical error and is corrected by the

corrected drawings submitted herewith, which correctly show "Gly" for the penultimate amino acid.

In addition, the sequence listing has also been amended, and a new computer-readable formatted file and substitute pages, along with a statement to support filing and submission according to 37 C.F.R. §§1.821-1.825 are being submitted herewith. With these corrections, the Owner requests that the objection be withdrawn.

### **1.3 Remarks about the Objections to the Claims (item 1.3)**

*Objection:* The Examiner objects to Claim 65 as a substantial duplicate of Claim 1.

*Remarks:* In this submission, Claim 1 has been amended and Claim 65 has been canceled, obviating the objection. The Examiner is therefore requested to remove this objection.

## **2 Remarks about the Rejections**

The removal of rejections to claims 4, 5, 11-15, 34, 71 and 72 and to claims 27, 34, 61, 65, 71, 80 and 81 are acknowledged.

**2.1 Rejection for indefiniteness:** The Examiner rejected claims under 35 U.S.C. § 112, second paragraph, (i) for lack of antecedent basis (Claim 11), (ii) for indefiniteness in using the term "a splice variant of human telomerase of SEQ ID No: 2" (Claims 1, 4, 11-15 and 101), (iii) for confusion about whether SEQ ID Nos: 35 and 52 are splice variants or truncations (Claims 1, 4, 65-67, 73-79, and 101), and (iv) for lack of antecedent basis of "reference human telomerase gene" (Claim 65).

*Remarks:* (i) Claim 11 has been amended to correct the error in antecedent basis. (ii) Claims 1, 4, and 11-15 have been amended to clarify that the splice variant refers to a DNA sequence that encodes SEQ ID No: 2 and Claim 101 has been canceled; (iii) As discussed above, SEQ ID Nos: 35 and 52 are splice variants. Due to the use of exon X, which creates a stop codon at the insertion site of exon X, the resulting proteins are shorter than the reference telomerase protein. For ease, these proteins are referred to as truncated in the N-terminal domain of human telomerase. (iv) Claim 65 has been canceled, obviating the rejection of this claim. Based on the claim amendments and remarks, the Examiner is requested to withdraw the rejections.

**2.2.1 Rejection for lack of written description.** The Examiner has rejected Claims

1, 4, 5-6, 11-15, 27, 61, 65-67, 73-79, 80-85, and 101 under 35 U.S.C. §112, first paragraph, for lack of written description.

*Remarks:* With due respect, the Owner strenuously disagrees with the Examiner, submitting that the specification contains adequate written description to support these claims. The reasons for adequate written description are largely stated in prior amendments and continue to apply. For the sake of brevity, the prior arguments are summarized here and attention is directed to the latest arguments put forth in the last Office Action (OA).

The claims are directed to an isolated nucleic acid molecule that encodes a splice variant of human telomerase. The specification on page 8, beginning at line 10, teaches the genus of splice variants of human telomerase that are intended to be encompassed by the present invention. The species of the genus include 128 splice variants that are taught by the present specification.

Applicants therefore strongly disagree with the Examiner's allegation that: "in the particular case of splice variants, none of the variants, or even tens of them, do not describe the structure and function of the genus, because one cannot establish only one function/structure relationship for the genus and thus the presence of a large number of species is still deemed to be not representative of the genus. Therefore, the specification has sufficiently described only those splice variants for which the complete structure is taught. OA at page 8. Furthermore, the Examiner states that "only those sequences which occur naturally are encompassed by the term "splice variant". Relying on Table 1, which exemplifies 32 different splice variants, the Examiner draws the inference that there is no evidence to suggest the remaining theoretical combinations occur in nature.

The written description requirement and guidelines, however, do not require that each and every "theoretical combination" be shown. Rather, the requirement may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, *or* by disclosure of relevant identifying characteristics. Furthermore, the guidelines explain that "a representative number of species means that the species which are adequately described are representative of the entire genus." Instead, the Examiner states, without providing specific evidence or detailed reasoning, that "additional members of the genus necessarily have structures which are different than that of other

members and will likely have different functions also, which functions are not predictable from the structure.” OA page 10. With due respect, this appears to be pure conjecture and an insufficient basis for the rejection. In contrast, the Owner contends that a representative number of species has been disclosed and thus, that the written description requirement is satisfied.

The Examiner also points to statements in the specification indicating, in her opinion, that the inventors realized that more splice variants are theoretically possible. As further support, the Examiner cites an article by Wick et al, which discloses the genomic structure of the human telomerase gene. Because the number of exons and introns in the Wick et al. reference does not jibe with the instant disclosure, the Examiner concludes that the complexity is greater than disclosed by Applicants and “therefore, the Applicants claim to all splice variants of human telomerase gene include subject matter not disclosed nor described in the specification.” OA at page 12. The Examiner uses these statements to support the conclusion that written description is not satisfied because some hypothetical variants are not described.

The Owner contends that the Examiner is raising a red herring of theoretical splice variants based on genomic structure and then using these theoretical splice variants to support the conclusion that the application does not adequately describe the genus. Earlier in the OA, the Examiner recognized that theoretical splice variants may not be actual splice variants when she made the statement: “merely because a particular arrangement is possible theoretically, does not mean it actually occurs in nature. Only those sequences which occur naturally are encompassed by the term “splice variant”. OA at page 9.

As noted above, the Examiner has asserted that there is no representative number of species for the genus of splice variants. The guidelines do not carve out exceptions for certain genera, and certainly do not exclude genera which have common structural and/or functional features. The members of the genus of splice variants of human telomerase share common structural features, i.e., shared sequence and alternative spliced patterns. The guidelines state that the written description requirement for a claimed genus may be satisfied through sufficient description of a *representative number* of species by actual reduction to practice. In the instant case, a large and representative number of species have been reduced

to practice, and each member of the species shares common structure and/or functional characteristics sufficient to demonstrate to one of skill in the art that the inventors had possession of the genus of human splice variants of telomerase.

Without acquiescing to the Examiner's arguments, and in the interest of advancing prosecution, the claims have been amended to claim only those splice variants that are specifically enumerated in the specification. Specifically, claim 1 now clearly indicates that the splice variants are combinations of the spliced exons that the inventors discovered. Furthermore, splice variants are clarified as identified relative to the reference telomerase sequence, SEQ ID No: 2. Support may be found on page 11, last paragraph, and Figure 1, for example. Therefore, the Examiner is requested to remove this rejection.

The Examiner further asserts that claims 5 and 11-15 are directed to a genus wherein no function for the genus is stated and members of the genus would be functionally diverse including species encoding an active telomerase, encoding inhibitors of telomerase activity, species useful in diagnosis of the telomerase related disorders, and species which lack any function, and the addition of functional language would alleviate this rejection. OA at page 12. Owner respectfully disagree with the Examiner's reasoning for this rejection. Claim 5 is directed to specific isolated nucleic acid molecules encoding specific splice variants of human telomerase. This claim additionally provides a function of the product of the specific sequences, namely that it binds telomerase RNA or has telomerase activity. Thus, the sequences are related not only by structure but also by function. Therefore, the Owner submits that these claims satisfy the written description requirement and requests that the Examiner remove the rejection.

The Examiner has alleged that claims 6, 61, and 80-85 lack sufficient written description because the claims lack functional language. OA at page 13-16. As above for claim 5, claim 6, 61, and 80-85 recite specific sequences and must be splice variants of human telomerase. These claims are supported by an adequate written description and further, claimed members of the genera are related to each other structurally, and thus fulfill the written description requirement. Without acquiescing to the Examiner's arguments, however, claims 6 and 61 have been amended to recite "consisting of", clearly defining the claimed sequences, and claims 80-85 have been canceled. Withdrawal of this rejection is

therefore respectfully requested.

The rejection of claims 67 and 101 as allegedly being directed to a genus of DNA molecules lacking the  $\alpha$  exon (A motif) for which the structure characteristic is allegedly missing in the claim is respectfully traversed. Applicants have (1) identified the gene encoding human telomerase, (2) the amino acid sequence of human telomerase and (3) identified motif A as being nearly identical to the  $\alpha$  exon. One of skill in the art would therefore understand that the genus which is claimed is one in which Applicants had possession. Further, both the specification and the general knowledge of those skilled in the art indicate that substantial common structure would be expected to be shared among isolated nucleic acid molecules encoding a human telomerase.

The Examiner also asserts that the total number of variants lacking the A motif is “probably greater” than that disclosed by the Applicants. OA at page 12. The Office has the burden of demonstrating lack of written description. The Examiner has not carried the burden because there are no facts to support the statement that the total number of variants lacking the A motif is “probably greater” than that disclosed by the Applicants. The citation of Wick et al. does not correct this deficiency because by the Examiner’s own admission, the best that Wick can suggest are hypothetical splice variants and hypothetical variants may not actually occur. Thus, the Examiner fails to provide evidence or sufficient reasoning that the claims fail to satisfy the written description requirement.

In the interest of advancing prosecution, however, claim 101 has been canceled and claim 67 amended to recite specific splice variants lacking the  $\alpha$  exon, rather than sequences encoding motif A. Cancellation of claim 101 should not be taken as acquiescence to the Examiner’s rejection, but is done solely for business purposes.

For the reasons noted above, the rejections under 35 U.S.C. § 112, first paragraph for allegedly failing to satisfy the written description requirement should be withdrawn.

**2.2.2 – Rejection for lack of scope of enablement:** Claims 1, 61, 65, 67, 73-79, 80-85 and 101 are rejected under 35 U.S.C. §112, first paragraph, for lack of enablement.

The rejection of claims 1, 2, 61, 65, 73-79, 80-85 and 101 under 35 U.S.C. § 112, first paragraph because the specification, while allegedly being enabling for the variant of human telomerase gene described by SEQ ID NO: 45, or fragments thereof that will

specifically hybridize to SEQ ID NO: 45 under defined conditions, allegedly does not provide enablement for any DNA molecule encoding any human telomerase variant, or any fragment and/or variants is respectfully traversed. The Examiner has stated that the claims are enabled for SEQ ID Nos: 1, 35, 37, 39, 42, 44, 46, 48, 50, 52-54, 56-58, 60-62, 64-66, 68-70, 72-74, 76-78, 80-82, and 84-86 but not any DNA molecule that comprises these molecules or that are at least 75% identical or hybridize to these molecules. Likewise, SEQ ID Nos: 18, 23, 25, 27, 29, 30, 32, and 33 are enabled but not for any DNA molecule comprising a sequence from this group or a variant or a molecule that hybridizes with these sequences.

As stated above, the Owner respectfully disagrees with the Examiner on the non-enabled molecules. On the basis of the telephone discussions, however, the claims have been amended to recite the SEQ ID Nos. Claim 1 has been amended to recite a combination of the exons that Applicants discovered are alternately spliced in and out of human telomerase RNA. The molecules of claim 1 are fully enabled by the specification in recitation of defined sequence. With these amendments, the Examiner is requested to remove the rejection. The Owner emphasizes though that deleting subject matter in the amended claims does not indicate acquiescence to the rejection.

**2.4 Rejection under 35 U.S.C. § 102.** The withdrawal of the rejections over Cech (I) is acknowledged. Claims 1, 4, 6, 11-15, 61, 65, 73-79 and 80-85 remain rejected as being anticipated by Cech, U.S. Patent No. 6,093,809 ("Cech II" or the '809 patent).

The rejection of these claims is respectfully traversed. The Owner respectfully requests that the Examiner review the cited Cech patent and its priority documents to confirm that the portions of the cited Cech patent is not only not entitled to the October 1996 priority date as stated by the Examiner, but is not entitled to a priority date earlier than the instant application. The Owner submits that information like this should lead one to make a determination of which new information in the CIPs are entitled to which filing dates. In its own review of the priority documents, the Owner finds that the Cech II patent does not disclose a splice variant of human telomerase prior to Applicants' priority date.

The Owner disagrees with the Examiner's continued rejection of these claims over sequences in Cech II. None of the cited sequences of the Cech patent are splice variants, while the instant claims require that molecules be splice variants. While the Owner contends

that the Cech patent does not anticipate the pending claims, the claims have been amended to put the application in condition for allowance in accordance with the discussions with the Examiners in August. The remarks below address the Examiner's rejections in light of the amendments presented herein.

Claim 1 is rejected as being anticipated by SEQ ID No: 225. SEQ ID No: 225 is the reference human telomerase, which is specifically excluded from the claims. The claims are directed to splice variants. By definition, the reference sequence is not a splice variant.

Claim 4 is rejected as anticipated by SEQ ID No: 224 as having more than 75% amino acid identity to SEQ ID NO: 46. Claim 4 has been amended to recite specific splice variants. None of the enumerated splice variants is identical to SEQ ID No: 224.

Claims 6, 11-15 and 61 are rejected as anticipated by nucleotides 2136-2221 of SEQ ID No: 224. As the claims have been amended to recite "consisting of" it is irrelevant if any of the claimed sequences are contained within the reference telomerase.

Claims 27-29 and 31 are rejected as anticipated by disclosure of oligonucleotides in the '809 patent that allegedly would hybridize to the claimed probes. The claims have been amended to recite specific probe sequences, none of which are disclosed in the '809 patent.

Claims 32 and 34 are rejected as anticipated by a set of thirteen primers presented in Table 3 of the '809 reference. This rejection is moot as the claims have been canceled.

Claims 80-85 are rejected as anticipated by a portion of SEQ ID No: 224. This rejection is obviated by the cancellation of these claims.

Claim 92 is rejected as anticipated by the same Table 3. Although claim 92 is canceled, Owner addresses this rejection as it might be applied to other claims presented herein. Even if Table 3 discloses oligonucleotides that could be chosen as from a Chinese menu and used to amplify across splice junctions, the Table does not either disclose specific primer pairs that are useful for the claimed amplifications nor does the specification disclose or suggest any reason to choose a particular primer pair. The primers were developed for determining a DNA sequence and not for amplifying splice variants. Moreover, as Cech II does not disclose or suggest splice variants, there is no motivation to use these primers for the claimed purposes.

The Examiner is therefore requested to remove the §102 rejection.

**2.4 Rejection for obviousness.** The Owner appreciates the Examiner removing this rejection.

**2.5 Obviousness type provisional double patenting rejection.** The Office has provisionally rejected claims 1, 2, 4-6, 11-15, 27-29, 31, 32, 34, 61, 65-67, 71-79, 80-85, 92-93 and 101 under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 65-87 of co-pending Application No. 09/108,401. The co-pending application has been abandoned, rendering this rejection moot.

**New claims 108-118.** Although no rejection has been made against these claims, these claims were discussed in the Examiner interviews. Similar, but not identical, claims were presented in the now-abandoned parent case, however, and were rejected under §102 and §103. The Owner will address here issues of patentability as might be restated against these claims, as was discussed with the Examiners. Claim 108 and its dependents are directed to nucleic acid molecules that encode the peptides of the various exons, exon 1, exon alpha, exon beta, and exon 3. As explained above and in previous amendments, Cech et al. did not disclose splice variants prior to the Applicants' priority date. With regard to exon 1 and exon 3, no sequence was disclosed by Cech. Exons alpha and beta are contained in the reference telomerase sequence, but that alone neither anticipates nor suggests the claimed sequences as there was no description, no isolation of, and no reason to isolate a nucleic acid molecule encoding these peptides. As discussed herein, exon alpha overlaps motif A, but is not identical in its boundaries and exon beta has no motif associated with it. Furthermore, the claim satisfies written description requirement for all the reasons stated above.

Claim 114 claims *pairs* of amplification primers that amplify the various exon sequences, with the further limitation that at least 15 nucleotides of each primer must be derived from the exon sequences. Again, because Cech et al. do not disclose telomerase splice variants, they do not disclose such primers or suggest any reason to choose such primer pairs, even for the alpha and beta exons, which are part of the reference telomerase sequence (see argument above).

Claims 116, 117 and dependents claim methods of determining patterns of expression of the RNA encoding telomerase. In the methods, cDNA is synthesized and amplified prior to hybridization of the amplified product with a probe derived from the exons

described in the instant specification. In claim 116, hybridization is effected with one or more probes and in claim 117, with two or more probes. Because Cech et al. did not recognize the existence of splice variants, no where in the prior art is the method disclosed or a suggestion of why such a method should be performed. Therefore, for the combination of probes claimed Cech fails to disclose or suggest these combinations. In addition, for claim 116, the regions used for probes are either sequences not disclosed by Cech et al. or for the beta exon, no oligonucleotide for the beta exon or reason to hybridize with that particular region. The beta exon is not associated with any described motif. Therefore, Owner submits that these claims are free of prior art.

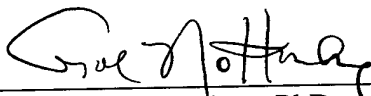
***Conclusion***

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. A full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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# N-terminal truncated telomerase

ATGCCGCGCTCCCCGCTGCCGAGCCGTCGCTCCCTGCTGCGCAGCCACTACCGCGAGGTGCTGCCGCTGGCCACGTTCTG  
M P R A P R C R A V R S L L R S H R E V L P L A T P V

CGGCGCTGGGGCCCCAGGGCTGGCGGTGGTGACGCGGGGACCGCGGCTTTCCGCGCTGGTGGCCAGTGCTGCTGCTGCGCTGGGACGACGCGCCCGCCCGCGC  
R R L G P Q G W R L V Q R G D P A A F R A L V A Q C L V C V P W D A R P P P A A

CCCCTCCTCCGCGAGGTCTCTGCTGAAGGAGCTGGTGGCCGAGTGCTGCAGAGGTGTGCGAGCGCGCGGAAGAACGTGCTGGCTTCGGCTTCGCGCTGCTGGACGGGGCCCG  
P S F R Q V S C L K E L V A R V L Q R L C E R G A K N V L A F G F A L L D G A R

CGGGGGCCCCCGAGGCTTCACCACGCGTGGCAGCTACCTGCCCAACACGGTGACCGACGCTGCGGGGAGCGGGGCTGGGGGCTGCTGCTGCGCGCGTGGCGACGACGT  
G G P P E A F T T S V R S Y L P N T V T D A L R G S G A W G L L L R R V G D D V

GCTGGTTCACCTGCTGGCAGCTGCGCGCTCTTTGTGCTGGTGGCTCCAGCTGCGCTACAGGTGTGCGGGGCGCGCTGTACCAGCTGCGCGCTGCCACTCAGGCCCCCGCCCGC  
L V H L L A R C A L F V L A R V L Q R L C E R G A K N V L A F G F A L L D G A R P P P

ACACGCTAGTGGACCCGAAAGCGTCTGGGATGCGAACGGGCTGGAACCATAGCGTGAGGAGCGGGTCCCCCTGGGCTGCCAGCCCCGGTGGAGGAGCGCGGGGAGTG  
H A S G P R R R L G C E R A W N H S V R E A G V P L G L P A P G A R R R G G S A

CAGCGAAGTCTGCGCTGCCAAGAGGCGCGGCTGCGCTGCGCTGAGCGGAGCGGACGCGCTGGGCGAGGGTCCCGGGCCAGGACGCGTGGACCGAGTGACG  
S R S L P L P K R L P R R G A A P E P E R T P V G Q G S W A H P G R T R G P S D R

TGGTTTCTGTGGTGTACCTGCGCAGACCGCGAAGAACCTCTTTGGAGGGTGGCTCTCTGGCACGCGCCACTCCACCCATCCGTGGGCGCGCAGCACCACGCGCGCCCGC  
G F C V V S P A R P A E E A T S L E G A L S G T R H S H P S V G R Q H H A G P P

ATCCACATCGCGGCCACCGCTCCCTGGGACACGCTTGTCCCCGCTGACGCGGAGACCAAGCACTTCTCTACTCTCAGGCGACAAGGAGCAGCTGCGGCGCTCTCTCTACTCAG  
S T S R P P R P W D T P C P P V Y A E T K H F L Y S S G D K E Q L R P S F L L S

CTCTCTGAGGCGCGCTGACTGGCGCTCGGAGGCTCGTGGAGACCATCTTTCTGGGTTCCAGGCGCTGGATGCCAGGACTCCCGCGAGTTGCCCCGCTGCCCCAGCGCTACTGCA  
S L R P S L T G A R R L V E T I F L G S R P W M P G T P R R L P R L P Q R Y W Q

AATGCGGCGCTGTCTCTGGAGCTGCTTGGGAACACGCGCAGTGCCCTACCGGGTGTCTCTCAAGACGCACTGCGCGCTGCGAGCTGCGGTACCCCGCAGCGCGGTCTGTGCCCG  
M R P L P L E L L G N H A Q C P Y G V L L K T H C P L R A A V T P A A G V C A R

GGAGAAGCCCCAGGCTCTGTGGCGGCCCCGAGGAGGAGACAGACCCCGCTGCGCTGGTGGCAGCTGCTCCGCGACACAGCAGCCCCGCGAGGTGTACGGCTTCGTGCGGCGCTG  
E K P Q G S V A A P E E E D T D P R R L V Q L L R Q H S S P W Q V Y G F V R A C

CCTGCGCGGCTGGTGGCGGCTTGGGCTCCAGGCACAACGAACCGCGCTTCTCAGGAACACCAAGAAGTTCATCTCCCTGGGGAAGCATGCCAAGCTCTCGTGCAGGAGCT  
L R R L V P P P G L W G S R H N E R R F L R N T K K F I S L G K H A K L S L Q E L

GACGTGGAAGATGAGCGTGGGACTGCGCTTGGCTGCGCAGGAGCCAGGGTGGCTGTGTTCCGCGCGCAGAGCACCGTCTGCGTGAGGAGATCTGCGCAAGTTCCTGCACTGGCT  
T W K M S V R D C A W L R R S P G V G C V P A A E H R L R E E I L A K F L H W L

GATGAGTGTGACGTCGTCGAGCTGCTCAGGTCTTTCTTTATGTACGGAGACACGTTTCAAAGAAGAGGTCTTGGAGCAAGTTGCAAGCATTTGG  
M S V Y V V E L L R S F F Y V T E T T F Q K N R L F F Y R K S V W S K L Q S I G

AAT--NNN--GACAGTCACCGGGGGTGGACCGCGACTGGGCGTCCCGAGGTTGACTATAGGACCAGGTGTCCAGGTGCCCTGCAAGTAGAGGGGCTCTCAGAGGCGTCTGGCTGG  
CATGGGTGGAGCTGGCCCCGGCATGGCTTCTGCGTGTGCTGCCGTGGGTGCCCTGAGCCCTCACTGAGTCGGTGGGGCTTGTGGCTTCCCGTGAGCTTCCCCCTAGTCTGTTGCTG  
GCTGAGCAAGCTCTCTGAGGGCTCTCTATTG...

FIG. 11A



# Truncated protein 1

ATGCCGCGCGCTCCCGCTGCCGAGCCGTGCGCTCCCTGCTGCGCAGCCACTACCGCGAGGTGCTGCCGCTGGCCACGTTCTG  
M P R A P R C R A V R S L L R S H R E V L P L A T F V

CGGCGCTGGGGCCCCAGGGCTGGCGGCTGGTGACGCGGGGACCCGCGGCTTTCCGCGCGTGGTGCCAGTGCCCTGGTGCGCTGGGACGACGCGCGCGCGCGC  
R R L G P Q G W R L V Q R G D P A A F R A L V A Q C L V C V P W D A R P P P A A

CCCTCCTTCGCCAGGTGCTGCTGAAGGAGCTGGTGGCCGAGTGCTGAGAGGCTGTCGAGCGCGCGCGAAGAACGCTGCTGGCTTCGGCTTCGCGCTGCTGGACGGGGCGCG  
P S F R Q V S C L K E L V A R V L Q R L C E R G A K N V L A F G F A L L D G A R

CGGGGCCCCCGAGGCTTCACCAACAGCGTGCAGCTACCTGCCCAACAGGTGACCGACGCACTGCGGGGAGCGGGGCTGGGGGCTGCTGCTGCGCGCTGGCGAGCAGCT  
G G P P E A F T T S V R S Y L P N T V T D A L R G S G A W G L L L R R V G D D V

GCTGGTTCACCTGCTGGCAGCTGCGCGCTCTTTGCTGGTGGTCCAGCTGCGCTACCAAGTGTGCGGCGCGCGCTGTACCACTGCGCGCTGCCACTAGCGCGCGCGCGCGC  
L V H L L A R C A L F V L V A P S C A Y Q V C G P P L Y Q L G A A T Q A R P P P

ACACGCTAGTGGACCCGAGGCGCTGCGGATGCGAAGCGGCTGGAACATAGCGTCAGGGAGCGCGGCTCCCTGGGCTGCCAGCGCGGCTGCGAGGAGCGCGCGCGCGCTG  
H A S G P R R R L G C E R A W N H S V R E A G V P L G L P A P G A R R R G G S A

CAGCGAAGTCTGCCGTTGCCAAGAGGCGCGGCTGCGCTGCGCGTGCAGCGGAGCGCGCGCTGGGCGAGGGTCTGGGCGCGCGCGCGCGCGCGCGCGCGCGC  
S R S L P L P K R P R R G A A P E P E R T P V G Q G S W A H P G R T R G P S D R

TGGTTCTGCTGGTGTCACTGCGCAGACCGCGAAGAACCACTCTTTGAGGGTGGGCTCTGTCGACGCGCGCGCGCGCGCGCGCGCGCGCGCGCGCGCGC  
G F P V V S P A R P A E E A T S L E G A L S G T R H S H P S V G R Q H H A G P P

ATCCACATCGCGGCGCGCGCTGCGGAGCGCGCTGCTCCCGGCTGTCGCGGAGACCAAGCACTTCTCTACTCTCAGCGGACAGGAGCGCGCGCGCGCGCGCGCGC  
S T S R P P R P W D T P C P P V Y A E T K H F L Y S S G D K E Q L R P S F L L S

CTCTGAGGCGCGCGCTGCTGCGGCTGCGGAGCGCGCTGCTGCGGAGCGCGCTGCTGCGGAGCGCGCGCGCGCGCGCGCGCGCGCGCGCGCGCGC  
S L R P S L T G A R R L V E T I F L G S R P W M P G T P R R L P R L P Q R Y W Q

AATGCGGCGCGCTGTTCTGAGGCTGCTGGGAAACCGCGAGTGCGCGCTACGCGGTGCTCCTCAAGACGCACTGCGCGCTGCGAGCTGCGGTACCGCGAGCGCGGTGCTGTCGCGC  
M R P L F L E L L G N H A Q C P Y G V L L K T H C P L R A A V T P A A G V C A R

GGAGAAGCGCGCGCTGCTGCGGCGCGCGGAGGAGGACACAGACCGC  
E K P Q G S V A A P E E E D T D P R R L V Q L L R Q H S S P W Q V Y G F V R A C

CCTGCGCGCGCTGTTGCCCGCGCGCTGCGGCTCCAGGCAACAAGCGCGCTTCTCAGGAACACCAAGAAGTTCTCTCCCTGGGAAGCATGCCAAGCTCTGCTGAGGAGCT  
L R R L V P P G L W G S R H N E R R F L R N T K K F I S L G K H A K L S L Q E L

GACGTGGAAGTGAAGCTGCGGAGCTGCGCTTGGCTGCGCAGGAGCGCGCGGTTGGCTGTTGCTCCGCGCGCAGAGCACCGCTGCGTGAGGAGATCCTGGCGAAGTTCTGCACTGGCT  
T W K M S V R D C A W L R R S P G V G C V P A A E H R L R E E I L A K F L H W L

GATGAGTGTACGTCGTCGAGCTGCTCAGGCTCTTTCTTTATGTCACGAGACCACTTTCAAAGAAGAGGCTCTTTTCTACCGGAAGAGTGTCTGGAGCAAGTTGCAAGCATTGG  
M S V Y V V E L L R S F F Y V T E T T F Q K N R L F F Y R K S V W S K L Q S I G

AATCAGACAGCACTTGAAGAGGTGAGCTGCGGAGCTGTCGAAGCAGAGGTGAGGAGCATCGGAAGCCAGGCGCGCGCTGCTGAGCTGAGACTCCGCTTCATCCCAAGCGCTGA  
I R Q H L K R V Q L R E L S E A E V R Q H R E A R P A L L T S R L R F I P K P D

GTGGCTGTGCTTTGGTTTAACTTCCTTTTAAACAGAA  
V A V L W F T F L P N Q K

CGGGCTGCGCGCGATTGTGAACATGGAATACGCTGCGGAGCGGAGCGCTTCCGCGAGAGAAAGAGGCGCGCGCGCTCTCAGGAGTGAAGGCACTGTTACGCGTGTCAACTACGA  
G L R P I V N M D Y V V G A R T P R R E K R P S V S F R G \*

FIG. 11B















N-terminal truncated telomerase (ver. 2)

ATGCCGCGCGCTCCCGCTGCCGAGCCGCTGCGCTCCCTGCTGCGCAGCCACTACCGCAGGTGCTGCCGCTGCCACGTTCTGT  
M P R A P R C R A V R S L L R S H ~~T~~ R E V L P L A T F V  
CGGCGCTGGGGCCCCAGGGCTGGCGGCTGGTGCAGCGCGGGGACCCGGCGGCTTCCGCGCGCTGGTGGCCAGTGCTGGTGTGCGTGCCTGGGACGCACGGCCGCCCCCGCGCG  
R R L G P Q G W R L V Q R G D P A A F R A L V A Q C L V C V P W D A R P P P A A  
GGCCTCCCCGGGGTGGCGCTCCGCTGGGGTTGAGGGCGGGGGGGAACAGCGACATGCGGAGAGCAGCGCAGGGGACTCAGGGCGCTTCCCCGCGAGGTG  
G L P G V G V R L G L R A A G G N Q R H A E S S A G D S G R F P R R  
A S P G S A S G W G \* G R P G G T S D M R R A A Q A T Q G A S P A G  
P P R G R R P A G V E G G R G E P A T C G E Q R R R L R A L P P Q V  
CCCCCTCTCCGCCAGGTGCTCCTGCCTGAAGAGCTGGTGGCCGAGTGCTGCAGAGGCTGTGCGAGCGCGCGGAAGAACGTGCTGGCTTCCGCTTCCGCTGCTGACGGGGCCG  
P S F R Q V S C L K E L V A R V L Q R L C E R G A K N V L A F G F A L L D G A R  
CGGGGCCCCCGGAGGCTTACCAACACGCTGCGCAGCTACCTGCCCAACAGCGTACCGACGCACTCGGGGAGCGGGGCTGGGGCTGCTGCTGCGCGCGTGGGCGACGACGT  
G G P P E A P R T L S V R T V T D A L R G S G A W G L L L R R V G D D V  
GCTGGTTCACCTGCTGGCAGCTGCGCGCTCTTTGTGCTGGTGGCTCCAGCTGCGCCTACAGGTGTGCGGGCGCGCTGTACAGCTCGCGCTGCCACTCAGGCCCGGGCCCCCGC  
L V H L L A R C A L F V L V A P S C A Y Q V C G P P L Y Q L G A A T Q A R P P P  
ACAGCTAGTGGACCCGAGGCGCTCTGGGATGCGAACGGGCTGGAACATAGCGTCAGGGAGCGCGGGTCCCTGGGCTGGGCTGCGAGGAGCGCGGGGCGAGCTG  
H A S G P R R R L G C E R A W N H S V R E A G V P L G L P A P G A R R R G G S A  
CAGCGAAGTCTGCGCTTCCCAAGAGGCGCAGCGCTGCGCTGCGCTGAGCGGAGCGGACGCGCTTGGCAGGGGCTCTGGGCGCCACCGGGCAGGACGCTGGAACGAGTGACCG  
S R S L P L P K R P R R G A A P E P E R T P V G Q G S W A H P G R T R G P S D R  
TGTTTCTGTGGTGTCACTGCCAGACCCCGGAAGAAGCCACTCTTTGGAGGGTGGCTCTCTGGCAGCGCCACTCCACCCATCCGTGGGCGCGCAGCACCAGCGGGCCCCC  
G F C V V S P A R P A E E A T S L E G A L S G T R H S H P S V G R Q H H A G P P  
ATCCACATCGCGGCCACCACTGCTCCGAGACGCGCTTGTCCCCGGTGTACGCGAGACCAAGCACTTCTCTACTCTCAGGCGACAAGGAGCAGCTGCGGCGCTCTCTACTCAG  
S T S R P P R P W D T P C P P V Y A E T K H F L Y S S G D K E Q L R P S F L L S  
CTCTCTGAGGCCAGCCTGACTGGCGCTCGGAGGCTCGTGAGACCATCTTTCTGGGTTCCAGGCGCTGGATGCCAGGACTCCCCGAGGTTGCGCGCTGCGCCAGCGCTACTGGCA  
S L R P S L T T G A R R L V E T I F L G S R P W M P G T P R R L P R L P Q R Y W Q  
AATGCGGCCCTGTTTCTGGAGCTGCTTGGGAACCAAGCGAGTGCCCTACGCGGTGCTCTCAAGACGCACTGCGCGTGCAGCTGCGGTACCCCGCAGCGCGGTGCTGTGCCG  
M R P L F L E L L G N H A Q C P Y G V L L K T H C P L R A A V T P A A G V C A R  
GGAGAAGCCCCAGGCTCTGTGGCGGCCCGGAGGAGGACACAGACCCCGTCCGCTGGTGCAGCTGCTCGCCAGCACAGCAGCCCTGGCAGGTGTACGGCTTCTGTGCGGGCTG  
E K P Q G S V A A P E E E D T D P R R L V Q L L R Q H S S P W Q V Y G F V R A C  
CCTGCGCGGCTGGTGGCCCCAGGCTCTGGGCTCCAGGCACAAGAACGCGCTTCTCAGGAACCAAGAAGTTCTCTCCCTGGGAAGCATGCCAAGCTCTCGCTGCAGGAGCT  
L R R L V P P G L W G S R H N E R R F L R N T K K F I S L G K H A K L S L Q E L  
GACGTGGAAGATGAGCGTGGGACTGCGCTTGGCTGCGCAGGAGCCAGGGGTTGGCTGTGTTCCGCGCGCAGACCGCTGCGTGAGGAGATCTCGGCAAGTTCTCTGCACTGGCT  
T W K M S V R D C A W L R R S P G V G C V P A A E H R L R E E I L A K F L H W L  
GATGAGTGTGACGCTGCTGAGCTGCTCAGTCTTTCTTTATGTACGGAGACCAAGTTTCAAAGAAGAGGCTCTTTTCTACCGGAAGAGTGTCTGGAGCAAGTTGCAAAGCATTGG  
M S V Y V V E L L R S F F Y V T E T T F Q K N R L F F Y R K S V W S K L Q S I G  
AAT--NNN--GACAGTCACCGGGGGTTGACCGCGGACTGGGCGTCCCAGGGTTGACTATAGGACAGGTGTCCAGGTGCCCTGCAAGTAGAGGGGCTCTCAGAGCGCTCTGGCTGG  
CATGGGTGGACGTGGCCCCGGGATGGCCTTCTGCGTGTGCTGCCGTGGGTGCCCTGAGCCCTCACTGAGTCGGTGGGGCTTGTGGCTTCCCGTGAGCTTCCCCCTAGTCTGTGTCTG  
GCTGAGCAAGCTCTCTGAGGGGCTCTCTATTG...

FIG. 11L

Truncated protein 1 (ver. 2)











